

is also provided on compact disc. Please amend the specification by inserting the Substitute Sequence Listing on the disc into the specification, in place of the Sequence Listing previously submitted. Please renumber the specification pages accordingly.

IN THE CLAIMS:

Please add new claims 75-147 as follows:

C 75. The recombinant vector according to claim 1, wherein the coding nucleotide sequence derived from a gene encoding a protein expression, export and/or secretion marker is a coding sequence derived from alkaline phosphatase *phoA* gene.

76. The recombinant vector according to claim 1, wherein the coding nucleotide sequence derived from a gene encoding a protein expression, export and/or secretion marker is a coding sequence of a gene for  $\beta$ -agarase, for a nuclease of a staphylococcus, or for a  $\beta$ -lactamase of a mycobacterium.

77. The recombinant vector according to claim 1, wherein the coding nucleotide sequence derived from a gene encoding a marker for the activity of promoters which are contained in the same fragment is a coding sequence derived from a firefly luciferase *luc* gene.

78. The recombinant vector according to claim 1, wherein the coding nucleotide sequence derived from a gene encoding a marker for the activity of promoters which are contained in the same fragment is a coding sequence derived from Green Fluorescent Protein *GFP* gene.

79. The recombinant vector according to claim 1, wherein the transcription terminator which is active in mycobacteria is a T4 coliphage terminator (tT4).

80. The recombinant vector according to claim 1, wherein the vector is a plasmid chosen from the following plasmids, which have been deposited at the CNCM (Collection Nationale de Cultures de Microorganismes, Paris, France):

a) pJVEDa which was deposited at the CNCM under the No. I-1797, on 12/12/1996;

b) pJVEDb which was deposited at the CNCM under the No. I-1906, on 25 July 1997; and

c) pJVEDc which was deposited at the CNCM under the No. I-1799, on 12/12/1996.

81. The recombinant vector according to claim 1, comprising at one cloning site of the polylinker a nucleic acid sequence of a mycobacterium in which detection is carried out of a polypeptide capable of being exported and/or secreted, and/or of being induced or repressed during infection with said mycobacterium or expressed or produced constitutively, as well as the associated promoter and/or regulatory sequences which are capable of allowing or promoting export and/or secretion of said polypeptide, or all or part of a gene encoding said polypeptide.

82. The recombinant vector according to claim 1, wherein the mycobacterial nucleic acid sequence which it contains is obtained by physical fragmentation or by enzymatic digestion of genomic DNA or of DNA which is complementary to an RNA of a mycobacterium.

83. The recombinant vector according to claim 1, wherein said mycobacterium is *M. tuberculosis*.

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84. The recombinant vector according to claim 1, wherein said mycobacterium is chosen from *M. africanum*, *M. bovis*, *M. avium* or *M. leprae*.

85. The recombinant vector according to claim 83, wherein the vector is a plasmid chosen from the following plasmids which have been deposited at the CNCM:

- a) p6D7, which was deposited on 28 January 1997 at the CNCM under the No. I-1814;
- b) p5A3, which was deposited on 28 January 1997 at the CNCM under the No. I-1815;
- c) p5F6, which was deposited on 28 January 1997 at the CNCM under the No. I-1816;
- d) p2A29, which was deposited on 28 January 1997 at the CNCM under the No. I-1817,
- e) pDP428, which was deposited on 28 January 1997 at the CNCM under the No. I-1818,
- f) p5B5, which was deposited on 28 January 1997 at the CNCM under the No. I-1819,
- g) p1C7, which was deposited on 28 January 1997 at the CNCM under the No. I-1820,
- h) p2D7, which was deposited on 28 January 1997 at the CNCM under the No. I-1821,
- i) p1B7, which was deposited on 31 January 1997 at the CNCM under the No. I-1843,

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j) pJVED/*M. tuberculosis*, which was deposited on 25 July 1997 at the CNCM under the No. I-1907, and

k) pM1C25, which was deposited on 4 August 1998 at the CNCM under the No. I-2062.

86. Recombinant vector according to claim 85, wherein the vector is plasmid pDP428, which was deposited on 28 January 1997 at the CNCM under the No. I-1818.

87. A method of screening nucleotide sequences derived from mycobacteria in order to determine a presence of sequences corresponding to exported and/or secreted polypeptides which may be induced or repressed during infection, their associated promoter and/or regulatory sequences which are capable in particular of allowing or promoting the export and/or secretion of said polypeptides of interest, or all or part of genes of interest encoding said polypeptides, comprising use of a vector according to claim 1.

88. The method of screening according to claim 87, comprising:

a) physical fragmentation of the mycobacterial DNA sequences or their digestion with at least one defined enzyme and recovery of the fragments obtained;

b) insertion of the fragments obtained in step a) into a cloning site, which is compatible, where appropriate, with the enzyme of step a), of the polylinker of a vector according to claim 1;

c) if necessary, amplification of said fragments contained in the vector, for example by replication of the latter after insertion of the vector thus modified into a defined cell, preferably *E. coli*;

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- d) transformation of host cells with the vector amplified in step c), or in the absence of amplification, with the vector of step b);
  - e) culture of transformed host cells in a medium allowing the detection of the export and/or secretion marker, and/or of the promoter activity marker which is contained in the vector;
  - f) detection of the host cells which are positive (positive colonies) for the expression of the export and/or secretion marker, and/or of the promoter activity marker;
  - g) isolation of the DNA from the positive colonies and insertion of this DNA into a cell which is identical to that in step c);
  - h) selection of the inserts contained in the vector, allowing the production of clones which are positive for the export and/or secretion marker, and/or for the promoter activity marker; and
  - i) isolation and characterization of the mycobacterial DNA fragments contained in these inserts, and it being possible for step i) to comprise, in addition, a step for sequencing the inserts selected.

89. A library of genomic DNA or of cDNA which is complementary to mycobacterial mRNA, wherein it is obtained by a method according to claim 87 and/or a method comprising steps a) and b) or a), b) and c) of the method according to claim 88.

90. The library of genomic DNA or of cDNA which is complementary to mycobacterial mRNA according to claim 89, wherein said mycobacterium is a pathogenic mycobacterium.

91. The library of genomic DNA or of cDNA which is complementary to mycobacterial mRNA according to claim 90, wherein said mycobacterium is a mycobacterium belonging to the *Mycobacterium tuberculosis* complex group.

92. The library of genomic DNA or of cDNA which is complementary to mycobacterial mRNA according to claim 91, wherein said mycobacterium is *Mycobacterium tuberculosis*.

C 93. A nucleotide sequence of mycobacterium or comprising a nucleotide sequence of mycobacterium selected by a method according to claim 87.

94. The nucleotide sequence of mycobacterium or comprising a nucleotide sequence of mycobacterium according to claim 93, wherein said mycobacterium is chosen from *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. avium*, *M. leprae*, *M. paratuberculosis*, *M. kansasii*, and *M. xenopi*.

95. The nucleotide sequence according to claim 93, chosen from  
SEQ ID NOS: 1, 8, 14, 25, 31, 33, 35, 41, 46, 52, 56, 62, 64, 67, 69, 72, 74, 76, 78, 81, 84, 86, 88, 90, 92, 96, 98, 100, 104, 106, 108, 110, 113, 119, 122, 128, 133, 137, 139, 141, 143, 145, 148, 150, 152, 154, 156, 158, 160, 162, 165, 169, 177, 184, 189, 195, 200, 202, 206, 209, 211, 213, 217, 220, 225, 228, 238, 246, 250, 255, 258, 260, 262, 268, 274, 278, 280, 282, 284, 286, 288, 290, 297, 310, 317, 321, 323, 325, 327, 331, 333, 335, 337, 339, 346, 347, 353, 357, 359, 361, 364, 368, 371, 374, 380, 383, 385, 387, 389, 393, 395, 397, 399, 403, 405, 407, 410, 412, 419, 421, 426, 429, 431, 433, 437, 441, 447, 452, 456, 459, 461, 463, 469, 472, 474, 476, 482, 485, 487, 489, 495, 497, 501, 505, 510, 516, 519, 522, 530, 534, 537, 544, 546, 550, 552, 554, 556, 558, 564, 569, 571, 573, 576, 580, 584, 586, 588, 590, 594, 596, 598, 600, 604, 608, 610,

612, 614, 616, 618, 620, 622, 624, 626, 629, 631, 633, 635, 640, 647, 649, 651, 653, 657, 660, 662, 664, 666, 669, 674, 676, 678, 683, 686, 691, 693, 695, 697, 702, 717, 728, 733, 736, 739, 741, 743, 746, 752, 755, 757, 759, 761, 764, 767, 769, 771, 784, 794, 805, 807, 809, 811, 813, 817, 821, 823, 825, 827, 831, 833, 835, 837, 839, 842, 844, 846, 848, 864, 878, 883, 885, 887, 895, 901, 907, and 909.

C. 96. The nucleotide sequence of mycobacterium according to claim 93, chosen from SEQ ID NOS: 1, 41, 88, 110, 122, 137, 158, 165, 530, and 544, which are contained respectively in the vectors pDP428 (CNCM, No. I-1818), p6D7 (CNCM, No. I-1814), p5F6 (CNCM, No. I-1816), p2A29 (CNCM, No. I-1817), p5B5 (CNCM, No. I-1819), p1C7 (CNCM, No. I-1820), p2D7 (CNCM, No. I-1821), p1B7 (CNCM, No. I-1843), p5A3 (CNCM, No. I-1815), and pM1C25 (CNCM, No. I-2062).

97. A nucleotide sequence comprising an entire open reading frame of a sequence according to claim 93.

98. A polynucleotide, comprising a polynucleotide chosen from:

- a) a polynucleotide whose sequence is complementary to the sequence of a polynucleotide according to claim 93;
- b) a polynucleotide whose sequence is at least 50% identical with a polynucleotide according to claim 93;
- c) a polynucleotide which hybridizes, under high stringency conditions, with a polynucleotide sequence according to claim 93; and
- d) a fragment of at least 8 consecutive nucleotides of a polynucleotide according to claim 93, or defined in a).

99. A polypeptide, its fragments or biologically active fragments or its homologous polypeptides, encoded by a mycobacterial nucleotide sequence according to claim 93, and which is exported and/or secreted, and/or induced or repressed, or expressed constitutively during an infection.

100. A recombinant mycobacterium transformed with a recombinant vector according to claim 1.

101. A polynucleotide chosen from SEQ ID NOS: 1, 8, 14, 25, 31, 33, and 35.

102. A polynucleotide comprising a polynucleotide chosen from:

a) a polynucleotide whose sequence is chosen from the nucleotide sequences SEQ ID NOS: 1, 8, 14, 25, 31, 33, and 35;

b) a polynucleotide whose nucleic sequence is the sequence between the nucleotide at position nt 964 and the nucleotide at position nt 1234, ends included, of the sequence SEQ ID NO: 1;

c) a polynucleotide whose sequence is complementary to the sequence of a polynucleotide defined in a) or b);

d) a polynucleotide whose sequence exhibits at least 50% identity with a polynucleotide defined in a), b) or c);

e) a polynucleotide which hybridizes, under high stringency conditions, with a sequence of a polynucleotide defined in a), b), c), or d); and

f) a fragment of at least 8 consecutive nucleotides defined in a), b), c), d) or e).

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103. The polynucleotide according to claim 20, wherein its nucleic sequence hybridizes with DNA of a sequence of mycobacteria and preferably with the DNA of sequences of mycobacteria belonging to the *Mycobacterium tuberculosis* complex.

104. A polypeptide encoded by a polynucleotide sequence according to claim 20.

105. A polypeptide comprising a polypeptide chosen from:

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a) a polypeptide whose amino acid sequence is included in an amino acid sequence chosen from SEQ ID NOS: 2-7, 9-13, 15-24, 26-30, 32, 34, 36-40, 42-45, 47-51, 53-55, 57-61, 63, 65-66, 68, 70-71, 73, 75, 77, 79-80, 82-83, 85, 87, 89, 91, 93-95, 97, 99, 101-103, 105, 107, 109, 111-112, 114-118, 120-121, 123-127, 129-132, 134-136, 138, 272-273, 140, 142, 144, 146-147, 149, 151, 153, 155, 157, 159, 161, 163-164, 166-168, 170-176, 178-183, 185-188, 190-194, 196-199, 201, 203-205, 207-208, 210, 212, 214-216, 218-219, 221-224, 226-227, 923-925, 229-237, 239-245, 247-249, 251-254, 256-257, 259, 261, 263-267, 269-271, 275-277, 279, 281, 283, 285, 287, 289, 291-296, 298-309, 311-316, 318-320, 322, 324, 326, 328-330, 332, 334, 336, 338, 340-345, 348-352, 354-356, 358, 360, 926-930, 362-363, 365-367, 369-370, 372-373, 375-379, 381-382, 384, 386, 388, 390-392, 394, 396, 398, 400-402, 404, 406, 408-409, 411, 413-418, 420, 422-425, 427-428, 430, 432, 434-436, 438-440, 442-446, 448-451, 453-455, 457-458, 460, 462, 464-468, 470-471, 473, 475, 477-481, 483-484, 486, 488, 490-494, 496, 498-500, 502-504, 506-509, 511-515, 517-518, 520-521, 523-527, 531-533, 535-536, 538-542, 543, 545, 547-549, 551, 553, 555, 557, 559-563, 565-568, 570, 572, 574-575, 577-579, 581-583, 585, 587, 589, 591-593, 595, 597, 599, 601-603, 605-607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 627-628, 630, 632, 634, 636-639, 641-

646, 648, 650, 652, 654-656, 658-659, 661, 663, 665, 931-933, 667-668, 670-673, 675, 677, 679-682, 684-685, 687-690, 692, 694, 696, 698-701, 703-716, 718-727, 729-732, 734-735, 737-738, 740, 742, 744-745, 747-751, 753-754, 756, 758, 760, 762-763, 765-766, 768, 770, 772-783, 785-793, 795-804, 806, 808, 810, 812, 814-816, 818-820, 822, 824, 826, 828-830, 832, 834, 836, 838, 840-841, 843, 845, 847, 849-863, 865-877, 879-882, 884, 886, 888-894, 896-900, 902-906, 908, and 910;

- b) a polypeptide homologous to the polypeptide defined in a);  
c) a fragment of at least 5 amino acids of a polypeptide defined in a) or b);

and

- d) a biologically active fragment of a polypeptide defined in a), b), or c).

106. A polypeptide whose amino acid sequence is included in the amino acid sequences SEQ ID NOS: 2-7, 9-13, 15-24, 26-30, 32, 34, or 36, or a polypeptide having the amino acid sequence SEQ ID NO: 543.

107. A polynucleotide encoding a polypeptide according to claim 105.

108. A nucleic acid sequence for use as a primer, wherein said sequence is chosen from the nucleic acid sequences of a polynucleotide according to claim 93.

109. A nucleic acid sequence according to claim 108, wherein said sequence is chosen from SEQ ID NO: 528 and SEQ ID NO: 529.

110. A nucleic acid sequence according to claim 108, for the detection and/or amplification of nucleic sequences.

111. A nucleic acid sequence which can be used as a probe, wherein said sequence is chosen from the nucleic acid sequences according to claim 93.

112. The nucleic acid sequence according to claim 111, wherein the nucleic acid sequence is labeled with a radioactive compound or with a nonradioactive compound.

113. The nucleic acid sequence according to claim 111, wherein the nucleic acid sequence is covalently or noncovalently immobilized on a support.

114. The nucleic acid sequence according to claim 111, for the detection and/or amplification of nucleic sequences.

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115. The nucleic acid sequence according to claim 111, wherein said sequence is a sequence between the nucleotide at position 964 and the nucleotide at position 1234, ends included, of the sequence SEQ ID No. 1.

116. A recombinant cloning, expression, and/or insertion vector, comprising a nucleic acid sequence of the polynucleotide according to claim 93.

117. A host cell transformed with a recombinant vector according to claim 116.

118. The host cell according to claim 117, wherein it is an *E. coli* strain transformed with the plasmid pDP428 deposited on 28 January 1997 at the CNCM under the No. I-1818, or wherein it is transformed with the plasmid pM1C25 which was deposited on 4 August 1998 at the CNCM under the No. I-2062, or wherein it is a strain of *M. tuberculosis*, *M. bovis* or *M. africanum* potentially possessing all the appropriate regulatory systems.

119. A method of preparing a polypeptide, comprising using a vector according to claim 116.

120. A recombinant polypeptide obtained by the method according to claim 119.

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121. A hybrid polypeptide comprising at least one polypeptide according to claim 99 and at least one polypeptide capable of inducing an immune response in humans or animals.

122. The hybrid polypeptide according to claim 121, wherein the polypeptide capable of inducing an immune response contains at least one antigenic determinant capable of inducing a humoral and/or cellular response.

123. A polynucleotide encoding the hybrid polypeptide according to claim 121.

124. The hybrid polypeptide according to claim 121, which is a recombinant protein obtained by the expression of a polynucleotide according to claim 123.

125. A method for the *in vitro* detection of antibodies directed against a mycobacterium, and preferably a bacterium of the *Mycobacterium tuberculosis* complex in a biological sample, comprising:

a) bringing the biological sample into contact with a polypeptide according to claim 99; and

b) detecting an antigen-antibody complex formed.

126. A method for the detection of an infection by a mycobacterium, and preferably a bacterium of the *Mycobacterium tuberculosis* complex in a mammal, comprising:

a) preparing a biological sample containing cells of said mammal, more particularly cells of the immune system of said mammal and still more particularly T cells;

b) incubating the biological sample of step a) with a polypeptide according to claim 99;

c) detecting a cellular reaction indicating prior sensitization of the mammal to said polypeptide in particular cell proliferation and/or the synthesis of proteins such as interferon-gamma; and

d) detecting a delayed hypersensitivity reaction or a reaction for sensitization of the mammal to said polypeptide.

127. A kit for the *in vitro* diagnosis of an infection by a mycobacterium belonging to the *Mycobacterium tuberculosis* complex, comprising:

- a) a polypeptide according to claim 99;
- b) where appropriate, the reagents for constituting the medium which is appropriate for the immunological reaction;
- c) the reagents allowing the detection of the antigen-antibody complexes produced by the immuno-logical reaction;
- d) where appropriate, a reference biological sample (negative control) free of antibodies recognized by said polypeptide; and
- e) where appropriate, a reference biological sample (positive control) containing a predetermined quantity of antibodies recognized by said polypeptide.

128. Mono- or polyclonal antibodies, fragments thereof, or chimeric antibodies, which specifically recognize a polypeptide according to claim 99.

129. An antibody according to claim 128, which is labeled.

130. A method for the specific detection of the presence of an antigen of a bacterium of the *Mycobacterium tuberculosis* complex in a biological sample, comprising:

a) bringing the biological sample into contact with an antibody according to claim 128; and

b) detecting an antigen-antibody complex formed.

131. A kit for the specific detection of the presence of an antigen of a bacterium of the *Mycobacterium tuberculosis* complex in a biological sample, comprising:

a) a polyclonal or monoclonal antibody according to claim 128;

b) a reagent for constituting the medium which is appropriate for the immunological reaction; and

c) at least one reagent allowing the detection of an antigen-antibody complexes produced by the immunological reaction.

132. A method for the detection and rapid identification of mycobacterium and preferably of *M. tuberculosis* in a biological sample, wherein it comprises the following steps:

a) isolating DNA from the biological sample to be analyzed, or producing a cDNA from RNA in the biological sample;

b) specifically amplifying DNA of mycobacteria belonging to the *Mycobacterium tuberculosis* complex with the aid of primers according to claim 108; and

c) analyzing amplification products.

133. A method for detecting bacteria belonging to the *Mycobacterium tuberculosis* complex in a biological sample, comprising:

a) bringing an oligonucleotide probe according to claim 111 into contact with a biological sample, the DNA contained in the biological sample having, where appropriate, been made accessible to the hybridization beforehand, under conditions

allowing the hybridization of the probe with the DNA of a bacterium of the *Mycobacterium tuberculosis* complex; and

b) detecting a hybrid formed between the oligonucleotide probe and the DNA of the biological sample.

134. A method for detecting bacteria belonging to the *Mycobacterium tuberculosis* complex in a biological sample, comprising:

a) bringing an oligonucleotide probe according to claim 40, immobilized on a support, into contact with a biological sample, DNA of the sample having, where appropriate, been made accessible to the hybridization beforehand, under conditions allowing the hybridization of the probe with the DNA of a bacterium of the *Mycobacterium tuberculosis* complex;

b) bringing a hybrid formed between the oligonucleotide probe immobilized on a support and the DNA contained in the biological sample, where appropriate after removal of the DNA of the biological sample which has not hybridized with the probe, into contact with a labeled oligonucleotide probe according to claim 112.

135. The method of detection according to claim 134, wherein, prior to step a), DNA of the biological sample, or cDNA obtained by reverse transcription of the RNA of the sample, is amplified using a pair of primers according to claim 108.

136. A method for detecting the presence of a bacterium belonging to the *Mycobacterium tuberculosis* complex in a biological sample, comprising:

a) bringing the biological sample into contact with a pair of primers according to claim 108, the DNA contained in the sample having been, where appropriate, made

accessible to hybridization beforehand, under conditions allowing hybridization of the primers with the DNA of a bacterium of the *Mycobacterium tuberculosis* complex;

b) amplifying DNA of the bacterium of the *Mycobacterium tuberculosis* complex;

c) detecting amplification of the DNA fragments corresponding to the fragment flanked by the primers, for example by gel electrophoresis or by using a labeled oligonucleotide probe according to claim 112.

137. A method for detecting the presence of a bacterium belonging to the *Mycobacterium tuberculosis* complex in a biological sample, comprising:

a) bringing the biological sample into contact with two pairs of primers according to claim 108, the DNA content in the sample having been, where appropriate, made accessible to hybridization beforehand, under conditions allowing hybridization of the primers with the DNA of a bacterium of the *Mycobacterium tuberculosis* complex;

b) amplifying DNA of the bacterium of the *Mycobacterium tuberculosis* complex;

c) detecting amplification of DNA fragments corresponding to the fragment flanked by said primers, for example by gel electrophoresis or by means of a labeled oligonucleotide probe according to claim 112.

138. A kit for detecting bacterium of the *Mycobacterium tuberculosis* complex in a biological sample, wherein it comprises the following components:

a) an oligonucleotide probe according to claim 111;

b) reagents necessary for carrying out a hybridization reaction; and



c) where appropriate, a pair of primers according to claim 108 as well as the reagents necessary for a reaction of amplification of the DNA (genomic DNA, plasmid DNA or cDNA) of a bacterium of the *Mycobacterium tuberculosis* complex.

139. A kit or box for the detection of the presence of a bacterium of the *Mycobacterium tuberculosis* complex in a biological sample, comprising:

- a) an oligonucleotide probe, termed capture probe, according to claim 113;
- b) an oligonucleotide probe, termed revealing probe, according to claim 111;
- c) where appropriate, a pair of primers according to claim 108, as well as the reagents necessary for a reaction of amplification of the DNA of a bacterium of the *Mycobacterium tuberculosis* complex.

140. A kit for the amplification of DNA of a bacterium of the *Mycobacterium tuberculosis* complex present in a biological sample, comprising:

- a) a pair of primers according to claim 108;
- b) reagents necessary for carrying out a DNA amplification reaction;
- c) optionally, a component which makes it possible to verify the sequence of the amplified fragment, more particularly an oligonucleotide probe according to claim 111.

141. An immunogenic composition, comprising at least one of a polypeptide according to claim 99, and a hybrid polypeptide according to claim 121.

142. A vaccine, comprising at least one of: a polypeptide according to claim 99 and a hybrid polypeptide according to claim 121, in combination with a pharmaceutically compatible vehicle and, where appropriate, one or more appropriate immunity adjuvants.

143. A vaccine for immunizing against a bacterial or viral infection, such as tuberculosis or hepatitis, comprising at least one of: a vector according to claim 116 and a polynucleotide according to claim 123, in combination with a pharmaceutically acceptable vehicle.

144. A vaccine comprising at least one of: a) one or more polynucleotide sequences according to claim 93 and b) one or more polynucleotides according to claim 98, in combination with a pharmaceutically compatible vehicle and, where appropriate, one or more appropriate immunity adjuvants.

145. A method of screening molecules capable of inhibiting the growth of mycobacteria or the maintenance of mycobacteria in a host, wherein said molecules block the synthesis or the function of the polypeptides encoded by a nucleotide sequence according to claim 93 or by a polynucleotide according to claim 98.

146. The method of screening according to claim 145, wherein the molecules are anti-messengers or induce the synthesis of anti-messengers.

147. A molecule capable of inhibiting the growth of mycobacteria or the maintenance of mycobacteria in a host, wherein said molecules are synthesized based on the structure of the polypeptides encoded by a nucleotide sequence according to claim 93 or by a polynucleotide according to claim 98.

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Please grant any extensions of time required to enter this amendment, and  
charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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